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The application of half-life in clinical decision making: Comparison of the pharmacokinetics of extended-release topiramate (USL255) and immediate-release topiramate

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ABSTRACT

Objective: For extended-release drugs with multi-compartment kinetics, such as topiramate, effective half-life ($t_{1/2eff}$) may be a more clinically relevant parameter than elimination half-life ($t_{1/2z}$). Using topiramate as a real-life example, the objective was to compare these half-life values for immediate- and extended-release topiramate (TPM-IR and USL255, respectively) to understand how drug pharmacokinetics may impact drug dosing recommendations.

Methods: The $t_{1/2z}$ and $t_{1/2eff}$ for USL255 and TPM-IR were compared using data from a phase I study (N = 36) of 200 mg USL255 administered once daily (QD) or TPM-IR twice daily (BID); effect of sampling duration on $t_{1/2z}$ was investigated. To further explore the relationship between half-life and dosing, steady-state PK was simulated for USL255 and TPM-IR.

Results: As previously reported, mean $t_{1/2z}$ was similar between USL255 (80.2 h) and TPM-IR (82.8 h); TPM-IR $t_{1/2z}$ was ∼4 times longer than reported in the Topamax label (21 h). In contrast, USL255 displayed a 1.5 fold longer $t_{1/2eff}$ (55.7 vs 37.1 h for TPM-IR). When $t_{1/2z}$ was calculated from 48 to 336 h, values ranged from 28.8 to 82.8 h. Simulated steady-state PK profiles of USL255 QD exhibited reduced plasma fluctuations during a dosing interval vs TPM-IR QD or BID.

Significance: As expected for the same moiety, $t_{1/2z}$ of USL255 and TPM-IR were similar; however, the longer $t_{1/2eff}$ for USL255 better approximates differences in recommend dosing (QD USL255 vs BID TPM-IR). Further, sampling duration impacted $t_{1/2z}$, diminishing its predictive value for determining dose regimens; sampling-time differences may also explain $t_{1/2z}$ discrepancy between TPM-IR here versus Topamax label. As expected, steady-state simulations confirm that although TPM-IR has a long $t_{1/2z}$, taking TPM-IR QD would lead to large plasma fluctuations. These data demonstrate that $t_{1/2z}$ may be less clinically meaningful than $t_{1/2eff}$, and using $t_{1/2z}$ for some drugs may lead to erroneous conclusions regarding dosing regimens.

1. Introduction

Appropriate interpretation of pharmacokinetic (PK) data is crucial when optimizing antiepileptic drug (AED) therapy. It is equally important that one not misapply either pharmacokinetic data, or the underlying mathematical principles of PK when constructing an individualized AED dosing regimen. One of the oldest, and most fundamental concepts in pharmacotherapy is that of drug half-life ($t_{1/2}$). The simple definition of $t_{1/2}$ is the time interval over which the amount of drug in the body is decreased by one-half. A common misconception is that $t_{1/2}$ is synonymous with clearance, which is not completely accurate. In fact, $t_{1/2}$ is a hybrid parameter that takes into account drug clearance as well as its volume of distribution (ie, drug distribution between plasma and the rest of the body after dosing). Therefore, a better way of viewing $t_{1/2}$ is that it is a predictor of drug accumulation and fluctuation in plasma concentration.

Clinicians may use $t_{1/2}$ to guide them in individualizing dosage regimens for patients. Understanding $t_{1/2}$ is particularly important when determining dosing intervals for chronically-administered

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drugs, as dosing adjustments may impact a drug's systemic exposure (ie, area under the concentration-time curve [AUC]) and plasma fluctuations. For example, if a drug is administered at a steady-state frequency equal to its $t_{1/2}$, then AUC during that dosing interval will be twice that seen following a single dose (Sahin and Benet, 2008); this is due to drug accumulation over time as a repeated dose is given prior to disappearance of the previous dose. Giving a drug more frequently than its $t_{1/2}$ will result in more drug accumulation, with the opposite occurring if that drug is given less frequently than the $t_{1/2}$ (Grover and Benet, 2011). With regards to plasma fluctuations, dosing a drug more frequently than its $t_{1/2}$ will result in a flatter plasma concentration-time curve (ie, less fluctuation) than if that same daily dose were being given less frequently (Grover and Benet, 2011).

Though half-life is a key pharmacokinetic parameter in determining drug dosing, it is important to note that drugs may exhibit multiple half-lives, depending on how they distribute into tissues throughout the body following dosing. As such, different methods can be used to calculate a drug's half-life. In practice, clinicians will often use *terminal elimination half-life* ($t_{1/2z}$) to guide drug dosing, as this is the most widely published half-life value and the one typically reported in prescribing information. The $t_{1/2z}$ for a drug is defined as drug elimination during the terminal phase, which is the final elimination phase following drug absorption and redistribution into body tissues.

For drugs with simple linear pharmacokinetics, $t_{1/2z}$ may be an accurate measure of a drug's half-life. However, for drugs with slower absorption, multi-compartment distribution into different tissues, and multi-exponential disposition, $t_{1/2z}$ may be a poor predictor of drug accumulation and fluctuation. This is illustrated in Fig. 1A, which depicts a hypothetical plasma concentration-time profile for a drug that distributes into multiple compartments. As $t_{1/2z}$ describes drug elimination during the terminal phase (*after* drug absorption and distribution has entirely completed), $t_{1/2z}$ may only describe a very small fraction of the plasma concentration-time curve (Bialer and Soares-da-Silva, 2012). Therefore, $t_{1/2z}$ will probably not describe concentration decline during a dosage interval for drugs with more complex absorption and distribution characteristics, such as extended-release formulations that are specifically designed to have a slower absorption profile. Another limitation of $t_{1/2z}$ is that the value can be impacted by PK assay methods, including sampling duration, assay sensitivity, and sampling frequency. For example, sampling duration (ie, the duration of time over which plasma samples are taken) can change the phase when half-life is measured, thereby impacting the resulting $t_{1/2z}$ value (Fig. 1A).

Given that most antiepileptic drugs (AEDs) will likely display multi-compartment kinetics, which half-life should the clinician use? If our clinical objective is to dose a drug that can be given as infrequently as possible, with minimal plasma concentration fluctuation and consistent exposure during the dosage interval, then use of the commonly accepted and published value of $t_{1/2z}$ may be incorrect for many AEDs. Indeed, using this value may result in suboptimal dosing predictions (Sahin and Benet, 2008). Therefore, a more clinically relevant half-life measure may be *effective half-life* ($t_{1/2eff}$), which describes the rate of drug loss across the entire dosing interval.

Unlike $t_{1/2z}$, which is calculated using the slope of the last drug elimination phase following single-dose administration (Fig. 1A; Eq. (1)), $t_{1/2eff}$ takes into consideration the entire concentration-time profile of a drug. The $t_{1/2eff}$ is calculated based on both the drug-dosing interval *and* drug accumulation over time following multiple-dose administration (Fig. 1B; Eq. (2)) (Boxenbaum and Battle, 1995). As a result, $t_{1/2eff}$ is expected to be less affected by sampling duration compared with $t_{1/2z}$, and its calculation only requires sampling over the dosing interval following a single dose

and at steady state. Thus, using $t_{1/2eff}$ to guide dosing may be particularly beneficial when long-term maintenance of therapeutic levels is required.

Overall, the use of $t_{1/2eff}$ in lieu of $t_{1/2z}$ may be particularly beneficial for extended-release AEDs with multi-compartment kinetics. Topiramate (TPM) is one such agent; Gidal and Lensmeyer demonstrated that TPM partitions in a saturable manner into erythrocytes (Gidal and Lensmeyer, 1999). The release of TPM from this high-affinity red blood cell compartment—presumably to carbonic anhydrase—likely contributes to reduced apparent oral clearance and volume of distribution at low concentrations (Shank et al., 2005). These properties of TPM make it an ideal candidate to compare the clinical utility of these two half-life measures.

Using TPM as a real-life example, the objective of this manuscript is to understand how the pharmacokinetics of immediate-release (IR) and extended-release (XR) formulations may impact drug dosing recommendations. First, the $t_{1/2eff}$ and $t_{1/2z}$ of IR and XR TPM will be compared to demonstrate how both formulation differences and methodology impact half-life values. Additionally, steady-state profiles will be simulated to understand how varying drug dosing (ie, once- vs twice-daily dosing) impacts the pharmacokinetics of IR versus XR formulations. Together, the use of TPM—an AED with IR and XR formulations—will demonstrate which half-life measure may be more clinically-useful in determining appropriate dosing intervals.

2. Methods

2.1. Comparison of elimination and effective half-Lives for USL255 and TPM-IR

The two TPM formulations evaluated were once-daily (QD) USL255, Qudexy® XR (topiramate) extended-release capsules (Upsher-Smith Laboratories, Inc. (Qudexy®, 2015)) and twice-daily (BID) IR topiramate (TPM-IR; Topamax®; Janssen Pharmaceuticals (Topamax®, 2009)). Half-life values were assessed from a phase I, randomized (N = 36), open-label, crossover study of single-dose USL255 200 mg and 2 doses of TPM-IR 100 mg dosed every 12 h (Lambrecht et al., 2011). The $t_{1/2z}$ and $t_{1/2eff}$ for USL255 and TPM-IR were previously calculated (Eqs. (1) and (2)) (Lambrecht et al., 2011). In brief, $t_{1/2z}$ is calculated by dividing the natural log of 2 by the slope of the last phase (λz), which is dependent on the blood sampling duration used for PK analyses (Fig. 1, Eq. (1)).

$$t_{1/2z} = \ln2/\lambda z \qquad (1)$$

In contrast, $t_{1/2eff}$ is calculated based on dosing interval (τ) and drug accumulation over time following multiple-dose administration (ie, drug accumulation index [Rac = steady-state $AUC_{0-\tau}$/single-dose $AUC_{0-\tau}$]; Eq. (2)).

$$t_{1/2eff} = \tau * \ln2/\ln[Rac/(Rac - 1)] \qquad (2)$$

To determine how the plasma sampling duration for PK calculations can impact half-life, $t_{1/2z}$ was calculated using data from the 48, 72, 168, 264, and 336 h PK sampling times of the phase I study for both USL255 and TPM-IR. Detailed information regarding participants and topiramate analyses are described in Lambrecht et al. (Lambrecht et al., 2011).

2.2. Simulated steady-state pharmacokinetic profiles for USL255 and TPM-IR

Simulations were used to predict steady-state plasma concentration-time profiles of USL255 administered QD and TPM-IR 200 mg administered QD or BID; approved dosing is QD for USL255 and BID for TPM-IR (Qudexy®, 2015; Topamax®, 2009).

A. Elimination Half-Life ($t_{1/2z}$)
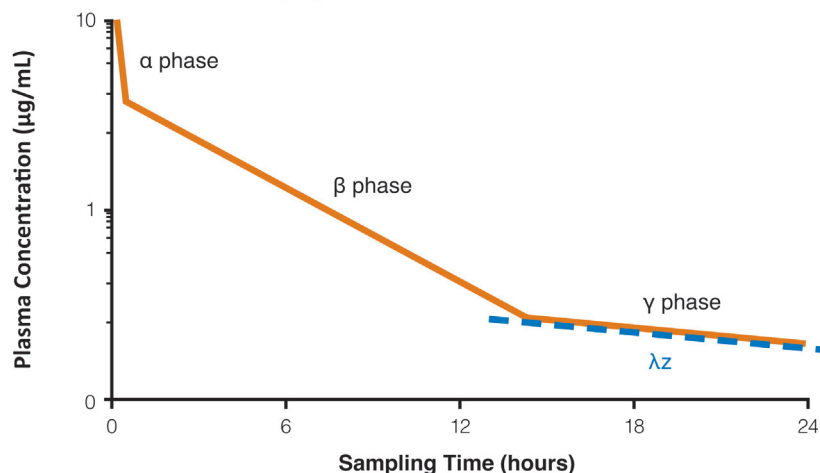
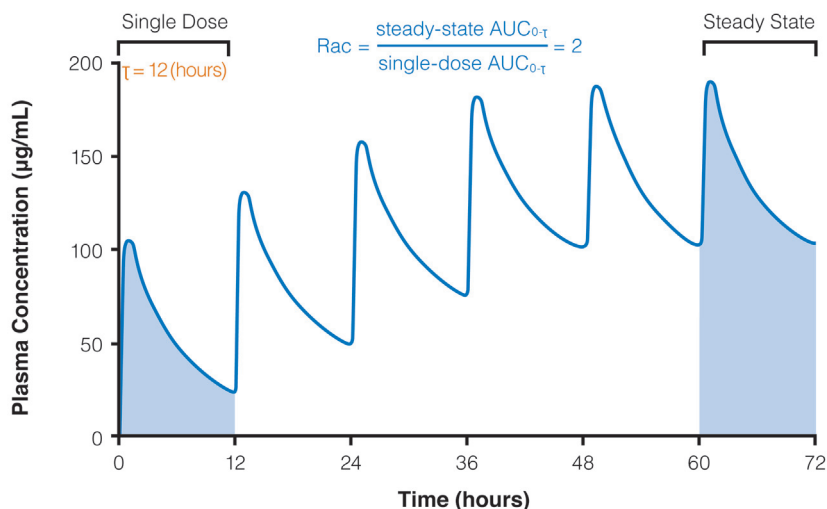## B. Effective Half-Life ($t_{1/2eff}$)

Fig. 1. Hypothetical Profiles Used to Calculate Elimination and Effective Half-Lives.

(A) Illustrated here is a hypothetical plasma concentration-time profile following a single dose of a 3-compartment drug. In the α phase, a rapid decrease in plasma levels is due to drug distribution from circulation (central compartment) into body tissues (peripheral compartments); this phase ends with pseudo-equilibrium of drug concentration between the central and peripheral compartments. The β phase describes a slower decrease in plasma drug levels due to drug metabolism and excretion from the body. The γ phase can occur later when tissue-bound drug is released into circulation then eliminated from the body; the γ phase may be associated with very small and insignificant amount of drug distribution. The slope of the last phase (λz) is used to calculate $t_{1/2z}$. In this example, the γ phase would be used, as the sampling duration extended to 24 h. If the sampling duration was only 12 h, the β phase would be used to calculate $t_{1/2z}$. Together, this figure illustrates how sampling duration may impact elimination half-life, and result in $t_{1/2z}$ estimates not being predictive of drug accumulation.

(B) Depicted is a hypothetical drug plasma accumulation following multiple doses of a drug dosed every 12 h. This graph describes the variables used to calculate $t_{1/2eff}$: drug dosing interval (τ) and drug accumulation index (Rac; steady-state $AUC_{0-\tau}$/single-dose $AUC_{0-\tau}$). AUC (area under the plasma concentration-time curve), is represented by the shaded boxes. In this hypothetical example, τ = 12 h and Rac = 2. Figure modified from Boxenbaum H and Battle M. Effective half-life in clinical pharmacology. *J Clin Pharmacol* 1995; 35:763–766 (Boxenbaum and Battle, 1995).

For USL255, a 2-compartment population PK model with sigmoid absorption and first-order elimination was developed from data obtained from 158 healthy male and female participants enrolled in four phase I studies (Bialer et al., 2013; Clark et al., 2014, 2016; Lambrecht et al., 2011). Covariate effects included allometric effects of weight on apparent oral clearance of topiramate (CL/F) and on apparent volume of distribution within the central compartment, and the effects of creatinine clearance on CL/F. TPM-IR was simulated using a modified 2-compartment linear population PK model with first order absorption as previously described (Girgis et al., 2010; Marathe, 2010). Covariate effects of weight on CL/F in the TPM-IR model were included.

Using the models described above, steady-state concentration-time profiles of USL255 QD and TPM-IR 200 mg/day QD or BID were simulated in a virtual population of 250 healthy individuals using NOMMEM® (ICON, Ellicott City, MD), and validated against observed data (Bialer et al., 2013). The virtual participant population for each formulation was generated through random re-sampling of participant characteristics in the USL255 model development dataset, keeping weight and creatinine clearance values together in the same individual. Steady-state simulations were used to compare the minimum observed drug plasma concentration (C_{min}), maximum observed drug plasma concentration (C_{max}), and fluctuation index ([$C_{max} - C_{min}$]/C_{avg}*100, where C_{avg} is the average drug plasma concentration) of USL255 and TPM-IR.

3. Results

3.1. Comparison of terminal and effective half-lives for USL255 and TPM-IR

The half-lives of USL255 and TPM-IR were evaluated in a prior phase I study of 36 healthy volunteers following a single dose of 200 mg USL255 QD and 200 mg TPM-IR BID (Lambrecht et al., 2011). As expected, the mean $t_{1/2z}$ was similar for USL255 and TPM-IR (80.2 h vs 82.8 h (Lambrecht et al., 2011)), despite differences in drug formulations and dosing recommendations. In contrast, the $t_{1/2eff}$ for USL255 was 1.5 fold longer than TPM-IR (55.7 h vs 37.1 h (Lambrecht et al., 2011)). This marked difference in $t_{1/2eff}$ between an immediate- and extended-release formulation is not unexpected, as effective half-life takes into account drug accumulation over the dose interval. Further, $t_{1/2eff}$ values were shorter than $t_{1/2z}$ for both USL255 and TPM-IR (55.7 vs 80.2 h for USL255 and 37.1 vs 82.8 h for TPM-IR, respectively).

3.2. Effect of sampling duration on terminal half-life values

For TPM-IR, mean terminal half-life of 82.8 h (Lambrecht et al., 2011), is almost 4-times longer than the 21 h value reported in the TPM-IR prescribing information (Topamax®, 2009). Because terminal half-life is dependent upon assay methodology, we investigated sampling duration as a factor for this large difference. Thus, $t_{1/2z}$ was calculated for USL255 and TPM-IR using different sampling durations from the dataset (Fig. 2). As sampling duration increased from 48 to 336 h, $t_{1/2z}$ increased for both USL255 and TPM-IR, independent of the formulation, with large ranges in value (USL255, 35.6–80.2 h; TPM-IR, 28.8–82.8 h). Interestingly, the 28.8 h half-life observed for TPM-IR at 48 h (Fig. 2) is in alignment with the 21 h half-life reported in the prescribing information, which was based upon a 32 h sampling time (Topamax®, 2009).

3.3. Simulated steady-state pharmacokinetic profiles for USL255 and TPM-IR

The simulated steady-state plasma concentration-time profiles for a typical individual receiving 200 mg/day USL255 or TPM-IR administered as a single 200 mg dose (QD) or two 100 mg doses (BID) are shown in Fig. 3. Validity of this simulation was supported by the similarity between observed steady-state phase I data of 200 mg/day USL255 QD and TPM-IR BID administered for 14 days (Bialer et al., 2013) and the simulated steady-state profiles. Based upon these simulations it is evident that although TPM-IR has a long $t_{1/2z}$ (>80 h), QD dosing based upon $t_{1/2z}$ would lead to large plasma fluctuations.

Evaluation of the recommended dosing regimen for USL255 and TPM-IR showed that mean predicted fluctuation index for USL255 QD was 18% lower than TPM-IR BID (0.23 vs 0.28), with a 47% decrease in the maximum fluctuation index (0.67 USL255 QD vs 1.27 TPM-IR BID). This difference is not unexpected, due to the greater predicted variability in C_{min} and C_{max} concentrations with TPM-IR BID compared with USL255 QD (Fig. 3; Table 1). Higher minimum plasma concentration for USL255 may have been a primary reason for this difference in fluctuation index, as mean predicted C_{min} for USL255 QD was 7.4% higher compared with TPM-IR BID, with little difference in mean predicted C_{max} (1.5% higher for USL255 vs TPM-IR; Table 1).

Though the comparison above included two drugs with different formulations (XR vs IR) and different dosing schedules (BID vs QD), similar trends are expected when keeping either formulation or dosing schedule consistent. For example, dosing XR and IR formulations on a similar schedule would be predicted to result in large fluctuation index differences; as expected, USL255 QD had a 65%

Table 1

Predicted steady-state PK parameters of USL255 and TPM-IR administered once or twice daily.

	USL255	TPM-IR	
	QD	BID	QD
C_{min}, μg/mL			
Mean (SD)	6.05 (1.53)	5.63 (1.74)	4.73 (1.99)
Median	5.96	5.62	4.51
Range	3.28–11.8	1.65–11.2	1.07–12.9
C_{max}, μg/mL			
Mean (SD)	7.60 (1.72)	7.48 (2.39)	9.04 (3.59)
Median	7.44	7.04	8.39
Range	4.20–13.8	2.14–16.8	1.68–25.7
Fluctuation Index			
Mean (SD)	0.23 (0.09)	0.28 (0.21)	0.66 (0.46)
Median	0.21	0.21	0.52
Range	0.06–0.67	0.07–1.27	0.08–2.42

Abbreviations: BID, twice daily; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; max, maximum; min, minimum; PK, pharmacokinetic; QD, once daily; SD, standard deviation; TPM-IR, immediate-release topiramate; USL255, extended-release topiramate.

lower mean predicted fluctuation index versus TPM-IR QD (0.23 vs 0.66; Fig. 3; Table 1). Similarly, dosing the same formulation more frequently would be predicted to reduce plasma fluctuations; as expected, BID administration of TPM-IR resulted in a 47% decrease in the mean predicted fluctuation index compared with QD dosing (0.28 vs 0.66; Fig. 3; Table 1). The reduced plasma fluctuation with BID dosing was due to a 19% higher mean predicted C_{min} and 17% lower mean predicted C_{max} versus QD dosing.

4. Discussion

Selection of an appropriate dosing interval is an important clinical decision. While many clinicians and clinical scientists have been taught that elimination half-life ($t_{1/2z}$) is the most useful parameter to guide dosing decisions (Sahin and Benet, 2008), this half-life value may not optimally characterize the steady-state concentration-time profile for many drugs (Dutta and Reed, 2006). A more appropriate parameter to predict drug accumulation and describe elimination at steady state may be effective half-life ($t_{1/2eff}$), which considers the entire plasma concentration-time profile of the drug and may better reflect total clearance (Boxenbaum and Battle, 1995). This may be particularly the case in situations where clinicians opt to use newer extended-release formulations of existing agents.

A goal of this manuscript was to use TPM as a real-life example to understand how drug PK—including half-life—may impact drug dosing recommendations. Results from these analyses suggest that half-life measures can be influenced by drug formulation (ie, XR and IR) and methodology (ie, PK sampling time). This was confirmed with observed data from TPM demonstrating that $t_{1/2z}$ is insensitive to formulation differences and varies depending on drug sampling time whereas $t_{1/2eff}$ may better approximate differences between XR and IR TPM.

When determining the impact of drug formulation on PK, one might think that an extended- and immediate-release formulation of the same active moiety would have different half-life values. However, the $t_{1/2z}$ for USL255 and TPM-IR are nearly identical (80.2 vs 82.8 h, respectively), and no large difference in $t_{1/2z}$ was observed between these 2 formulations when sampling time was kept consistent (Fig. 2). This similar $t_{1/2z}$ for USL255 and TPM-IR may lead to the incorrect assumption that changes in plasma concentration over 24 h are similar between XR and IR formulations or that IR drugs may be dosed less frequently. In contrast, the 1.5-fold higher $t_{1/2eff}$ for USL255 versus TPM-IR (55.7 vs 37.1 h) better
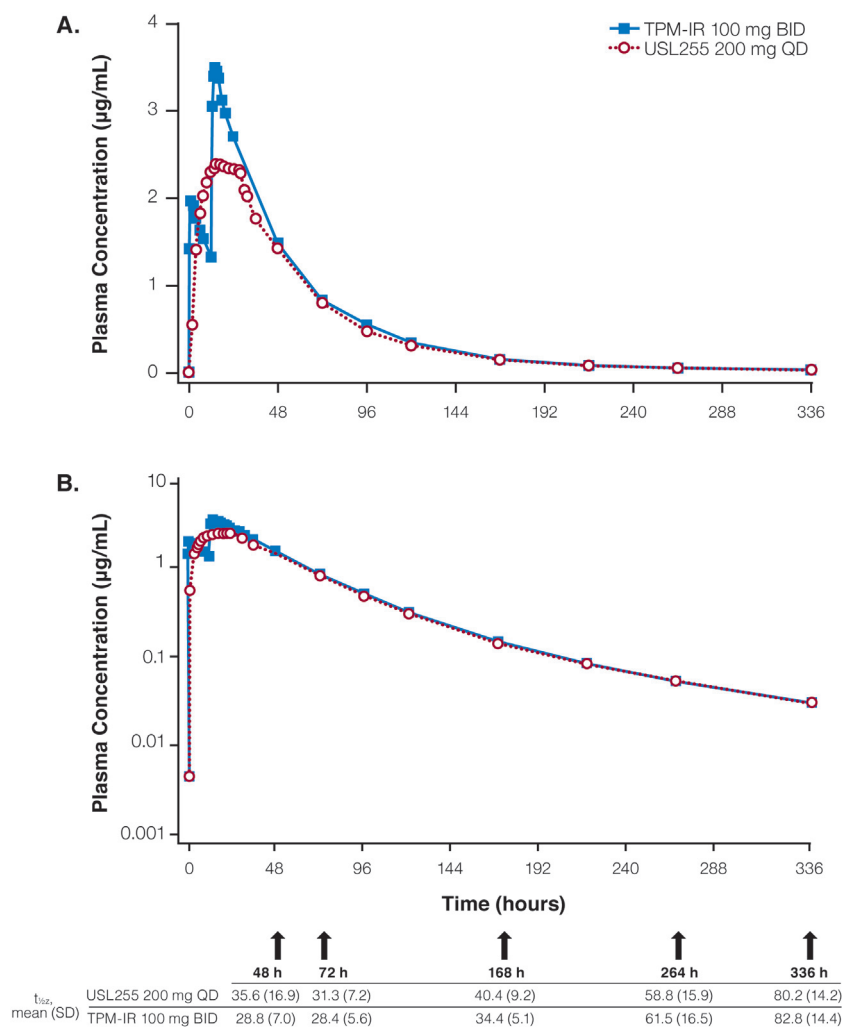
Fig. 2. Impact of Pharmacokinetic Sampling Duration on Elimination Half-Life of 200 mg USL255 and TPM-IR.

$t_{1/2z}$ calculated at each sampling duration (black arrows) for 200 mg/day USL255 and TPM-IR is presented under the concentration-time profile for both topiramate formulations. Linear scale is shown in panel A and log scale shown on panel B. Samples for TPM-IR were taken following the 2nd BID dose (eg, 48 h equals 36 h post 2nd dose, 72 h equals 60 h post 2nd dose, etc). Figure was modified from Lambrecht LJ et al. Comparative pharmacokinetic analysis of USL255, a new once-daily extended-release formulation of topiramate. *Epilepsia* 2011;52(10):1877–83 (Lambrecht et al., 2011).

Abbreviations: BID, twice daily; QD, once daily; $t_{1/2z}$; elimination half-life; TPM-IR, immediate-release topiramate; USL255, extended-release topiramate.

approximates the difference in recommend dosing between the 2 formulations (QD vs BID, respectively). Similar results for other AEDs also have demonstrated that $t_{1/2eff}$ may be more clinically meaningful than $t_{1/2z}$. Dutta and Reed demonstrated that although valproic acid has a $t_{1/2z}$ of 12–16 h, the $t_{1/2eff}$ of divalproex-ER over a dosage interval was in fact 40 h (due to its prolonged drug release), supporting its once-per-day administration (Dutta and Reed, 2006). Likewise, for the AED eslicarbazepine acetate, $t_{1/2eff}$ corresponds well with its once-daily dose interval. Based upon its absorption rate as well as metabolite formation rate and dosage interval, eslicarbazepine accumulation ratio translated into an $t_{1/2eff}$ for eslicarbazepine of 20–24 h, or about twice as long as its $t_{1/2z}$ (Bialer and Soares-da-Silva, 2012).

In addition to being unaffected by drug formulation differences, $t_{1/2z}$ can also be impacted by clinical methodology. As described above, the 82.8-h $t_{1/2z}$ reported for TPM-IR (Lambrecht et al., 2011) is almost 4-times longer than the 21-h value reported in the TPM-IR label (Topamax®, 2009). Though the half-life value from Lambrecht et al. may seem contradictory to the Topamax prescribing information, this discrepancy in $t_{1/2z}$ is likely due to methodology and not due to an actual difference in half-life. For example, the sensitivity of the PK assay was increased for Lambrecht and colleagues

versus the Topamax prescribing information (10 ng/mL lower limit of quantification [LLOQ] vs 500 ng/mL LLOQ, respectively); further, Lambrecht et al. had a longer sampling duration (336 vs 32 h, respectively). To demonstrate how sampling time can impact $t_{1/2z}$, TPM-IR and USL255 were evaluated at various time points. As sampling duration increased from 48 to 336 h, the $t_{1/2z}$ also increased from approximately 30 to 80 h (Fig. 2). It is important to note that this large impact of sampling time on $t_{1/2z}$ is not a universal feature for all drugs; for TPM, its multi-compartment PK may make it more sensitive to sampling time compared with a drug that does not distribute into multiple tissue compartments (see Fig. 1A for a hypothetical example on how sampling time may impact $t_{1/2z}$).

Taken together, these data suggest that $t_{1/2z}$ may not accurately represent a clinically meaningful elimination or accumulation estimate of an extended-release drug, and use of $t_{1/2z}$ may result in an inaccurate prediction of the appropriate dosing interval.

A limitation of these analyses is the evaluation of PK in healthy individuals and not patients with epilepsy; as such, specific factors that may influence PK may not be represented (eg, concomitant use of cytochrome inducers or inhibitors). FDA guidance often recommends PK analyses in healthy individuals, which may limit confounding factors, and data from healthy individuals are often
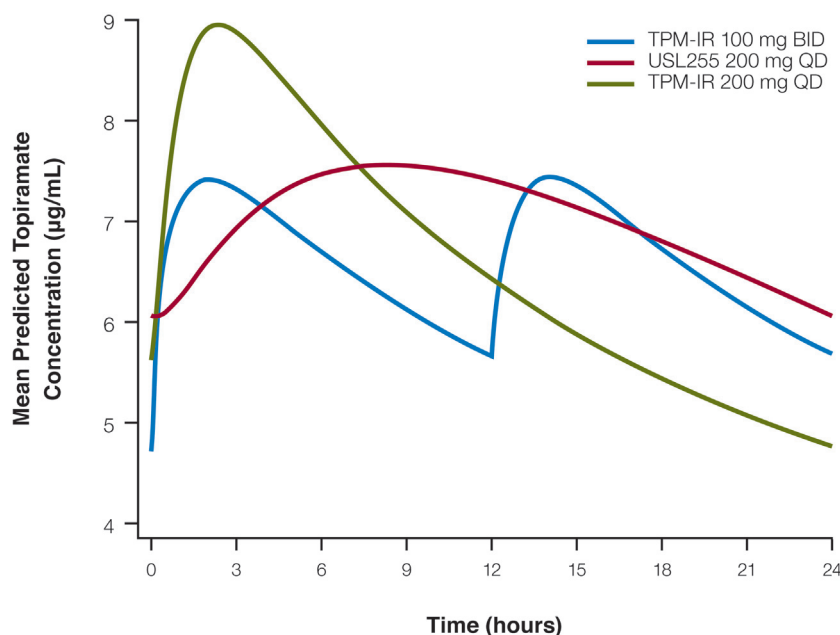
Fig. 3. Mean Predicted Steady-State Plasma Topiramate Concentrations of USL255 and TPM-IR Administered QD or BID.
Simulated steady state based on mean predicted plasma concentration-time profiles for 200 mg/day USL255 and TPM-IR once- or twice-daily are shown.
Abbreviations: BID, twice daily; QD, once daily; TPM-IR, immediate-release topiramate; USL255, extended-release topiramate.

used in modeling analyses to evaluate drug PK. Further, results from these analyses were not intended to serve as direct clinical outcome data. A detailed comparison of $t_{1/2z}$ and $t_{1/2eff}$—using TPM as a real-life example—was used to illustrate how formulation and methodological differences may impact half-life values, which has implications in patient care.

For example, in cases where clinicians choose to implement a dosing schedule that differs from the approved dosing recommendations of a given drug, understanding half-life is particularly important. For patients who are already on concomitant BID drugs, some clinicians may recommend taking the same total daily dose of a QD drug (with a long half-life) twice daily to potentially reduce plasma fluctuations and simplify the overall drug regimen. Conversely, a clinician may assume that a BID drug with an ∼24-h half-life could be administered QD. For example, the 21-h reported $t_{1/2z}$ for TPM-IR (Topamax®, 2009) may be interpreted to mean QD dosing is acceptable. However, QD dosing may not be optimal based on the predicted steady-state profile of TPM-IR, which showed increased plasma fluctuations compared with TPM-IR BID (Fig. 3). These data, using TPM as an example, underscore the importance of understanding the clinical relevance of half-lives reported in a drug's prescribing information. Additionally, while half-life may be one parameter used to guide dosing, assessing the entire steady-state profile may provide additional information when optimizing a dosing regimen.

It is important to note that neither $t_{1/2z}$ nor $t_{1/2eff}$ for USL255 and TPM-IR are identical to recommended dosing intervals for these drugs. This is because half-life alone may not provide all of the information necessary to construct an appropriate dosing regimen, as additional pharmacodynamic effects of a drug (eg, therapeutic index and receptor binding affinity/duration of binding) may influence drug distribution. Additionally, drugs can be dosed more frequently than recommended by half-life values, as dosing may be optimized to decrease fluctuations in plasma concentrations.

USL255 was developed to provide relatively consistent plasma drug concentrations across a 24-h dosing interval with reduced fluctuations compared with TPM-IR (Bialer et al., 2013). This is supported by the steady-state simulations shown here, which revealed that USL255 QD had a smaller fluctuation index and higher C_{min} than TPM-IR QD or BID (Fig. 3). The mean predicted fluctuation index for USL255 QD was reduced by 18% compared with TPM-IR BID, which is slightly lower than the observed 26% decrease in fluctuation index with USL255 QD versus TPM-IR BID following steady-state dosing in healthy volunteers (Bialer et al., 2013). This difference may be due in part to limitations in our methodology; while data from the Bialer et al. study were used to estimate $t_{1/2eff}$ for USL255 and TPM-IR, the models used here were from the literature. Therefore, the profiles in this analysis were developed using 2 different data sets (ie, not the same participants).

The predicted steady-state profiles for USL255 and TPM-IR provide a better understanding of XR versus IR topiramate PK, which may be considered when determining drug choice and dosing. In general, XR AEDs tend to have reduced plasma fluctuations and flatter plasma concentration-time curves than their IR counterparts (Pellock et al., 2004), a pattern that also was observed for USL255 and TPM-IR. A flatter steady-state curve for XR AEDs may be favorable for patients who require dosing adjustments, particularly increased doses, to maintain seizure control without precipitating any adverse events associated with peak concentrations (Pellock et al., 2004).

5. Conclusions

The commonly referenced elimination half-life ($t_{1/2z}$) may not be adequate or appropriate in many circumstances. Effective half-life, or $t_{1/2eff}$, may indeed be more clinically relevant as it takes into consideration the entire concentration-time profile of a drug. This is particularly true when comparing dosing requirements between immediate and extended-release product formulations. However, half-life is not the only parameter used to determine dosing regimens. The importance of recommended dosing from prescribing information is illustrated by the simulations of TPM-IR; while once-daily dosing may seem appropriate with its long reported half-life, doing so may result in large plasma fluctuations. Together with the comparison of $t_{1/2eff}$ and $t_{1/2z}$, these data underscore the

importance of understanding half-life measures, and may improve clinicians' understanding of dosing regimens.

Disclosures

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